Original Article

Weaning of mechanically ventilated chronic obstructive pulmonary disease patients by using non-invasive positive pressure ventilation: A prospective study

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) patients frequently pose difficulty in weaning from invasive mechanical ventilation (MV). Prolonged invasive ventilation brings along various complications. Non-invasive positive pressure ventilation (NIPPV) is proposed to be a useful weaning modality in such cases. **Objective:** To evaluate the usefulness of NIPPV in weaning COPD patients from invasive MV, and compare it with weaning by conventional pressure support ventilation (PSV). **Materials and Methods:** For this prospective randomized controlled study, we included 50 COPD patients with type II respiratory failure requiring initial invasive MV. Upon satisfying weaning criteria and failing a t-piece weaning trial, they were randomized into two groups: Group I (25 patients) weaned by NIPPV, and group II (25 patients) weaned by conventional PSV. The groups were similar in terms of disease severity, demographic, clinical and biochemical parameters. They were compared in terms of duration of MV, weaning duration, length of intensive care unit (ICU) stay, occurrence of nosocomial pneumonia and outcome. **Results:** Statistically significant difference was found between the two groups in terms of duration of MV, weaning duration, length of ICU stay, occurrence of nosocomial pneumonia and outcome. **Conclusion:** NIPPV appears to be a promising weaning modality for mechanically ventilated COPD patients and should be tried in resource-limited settings especially in developing countries.

KEY WORDS: Chronic obstructive pulmonary disease, invasive mechanical ventilation, non-invasive positive pressure ventilation, weaning

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INTRODUCTION

Weaning from invasive mechanical ventilation (MV) may be defined as the process of abrupt or gradual withdrawal of ventilator support, thereby shifting the work of breathing from machine to man. More than 40% of the time that a patient spends on MV is constituted by the weaning period, and around 20% of mechanically ventilated patients will fail their first attempt at weaning.[1,2] The corresponding figures for patients of chronic obstructive pulmonary disease (COPD) are 59%[3] and 50%,[4] respectively. Thus, achieving a careful balance between early versus delayed weaning is a must to minimize the risk of complications associated with either of the two. Premature discontinuation of MV may result in cardio-respiratory failure.[5] Moreover, overloading and fatigue of respiratory muscles together with an inability to protect the airway leads to reintubation. The latter by itself is associated with an increase in morbidity, mortality,[6] duration of MV, and length of intensive care unit (ICU) and hospital stay.[7] On the other hand, if initiated late, weaning may be unsuccessful because of respiratory muscle weakness caused by deconditioning

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and disrupted breathing regulation.[8] Further, prolonged MV, as often seen in COPD patients, is itself associated with complications like nosocomial pneumonia, cardiac morbidity, gastrointestinal bleeding, deep vein thrombosis and death. Thus, choosing the right time and right weaning strategy forms a crucial part of the management of such critically-ill patients and certainly affects their outcome.

Several studies have been conducted previously to compare different weaning methods for patients on MV, with variable results. Two large randomized controlled trials (RCTs) conducted separately by Brochard *et al.*,[9] and Esteban *et al.*,[10] have found the superiority of pressure support ventilation (PSV) and t-piece, respectively, over other methods of weaning. However, these studies do not help in arriving at a consensus regarding the best mode of weaning.

The present study was conducted with the objective to compare the usefulness of NIPPV with conventional PSV as two different weaning modalities in mechanically ventilated COPD patients.

MATERIALS AND METHODS

This prospective, two-group, parallel RCT was conducted in the ICU of a tertiary care referral medical institution of north India over a period of 18 months. The study protocol was approved by the ethics committee of the hospital and informed consent was taken from the patients' kin.

Known cases of COPD (confirmed clinico-radiologically and with available pulmonary function test (PFT) reports) who were admitted to our ICU in an acute exacerbation requiring endotracheal intubation (ETI), were eligible for the study. Type II respiratory failure was defined as sudden, severely worsened dyspnoea without any other obvious cause and with room-air arterial blood gas (ABG) analysis showing pH <7.35, arterial partial pressure of carbon dioxide ($PaCO_2$) >45 mm Hg and arterial partial pressure of oxygen (PaO_2) <60 mm Hg.

Major criteria for ETI[11] were respiratory arrest, loss of consciousness/gasping for breath, psychomotor agitation requiring sedation, heart rate (HR) <50 beats/min with loss of alertness, and hemodynamic instability with arterial systolic blood pressure (SBP) <70 mm Hg or >180 mm Hg. Minor criteria[11] were a respiratory rate (RR) >35 breaths/min, arterial pH <7.30, (PaO_2) <45 mm Hg despite supplemental oxygen, worsened neurological status (encephalopathy score) and inability to expectorate due to weakened cough reflex. The presence of one major criterion before initiating treatment or two minor criteria an hour after initiation of treatment was considered as an indication for ETI.

Non-intubated COPD patients were excluded from the study, as were those having neurological alteration unrelated to hypercapnoeic encephalopathy, cranio-facial deformity, upper airway obstruction, cardiogenic pulmonary edema, cardiac arrest, cardiogenic shock, acute myocardial infarction, pneumonia, pneumothorax, pulmonary neoplasm, pulmonary thromboembolism, gastrointestinal bleeding, and post-operative respiratory failure.

All subjects were evaluated by thorough history taking, clinical examination, chest radiography, ABG analysis, and other routine hematological investigations, as needed. ABG was done at 0, 1, 4, 8, and 12 hours after initiation of MV and also during weaning when required. Glasgow coma scale (GCS) scoring was done at presentation and reassessed periodically. Similar medications were used in all patients depending upon their requirement, like intravenous antibiotics, bronchodilators, corticosteroids, aerosolized bronchodilators and corticosteroids, correction of electrolytes and intravascular volume abnormalities. Orotracheal route was utilized for ETI and control mode of ventilation/assist control mode of ventilation (CMV/ACV) was used initially for mechanical ventilation, depending upon the patients' mentation and ABG parameters. Ventilator settings used were RR – 12-16/min, tidal volume 8-10 mL/kg, inspired oxygen fraction (FiO_2) to achieve an oxygen saturation (SaO_2) of 90% with a positive end-expiratory pressure (PEEP) of 5 cm H_2O, and an inspiratory: Expiratory ratio of 1:2-2.5. Use of muscle relaxants and sedatives was limited to an 'as and when required' basis.

Weaning criteria[12] used when giving an initial t-piece trial to patients were: An adequate mentation and cough reflex, clinical stability, and adequate oxygenation as reflected by SaO_2 of >90% at FiO_2 ≤0.4, after at least 48 hours of invasive MV. Criteria for failure of the t-piece trial were[13] pH <7.35, PaO_2 <50 mm Hg at FiO_2 of 0.4, RR >35/min, HR >145/min, SBP >180 mm Hg or <70 mm Hg, severe cardiac arrhythmias, agitation/anxiety/diaphoresis.

Complete rest was given to patients who failed the initial t-piece trial by putting them back on CMV/ACV mode of ventilation till previous pH and $PaCO_2$ values were attained and RR was ≤30/min. Thereafter, the patients were considered for weaning and randomized into two groups–group I, weaned by NIPPV; and group II, weaned by invasive PSV. The randomization was done by using two closed, non-transparent identically looking envelopes,[5,9,11,14] each containing information on one of the weaning methods being investigated. After a patient was included in the study, a third party not involved in the study was asked to choose one of the envelopes. Depending on the information in the chosen envelope, the patient was allocated to undergo weaning by either of the two methods.

Following randomization, group I patients were extubated and applied NIPPV with a full-face mask using Bilevel Positive Airway Pressure (BiPAP) system (RESMED, VPAP III STA). NIPPV was given 24 hours/day except during meals and for expectoration. Initial levels of inspiratory

and expiratory positive airway pressure (IPAP and EPAP respectively) were decided on the basis of achieving acceptable ABG parameters, RR <25/min, and patient's tolerance and comfort. Further adjustment in BiPAP setting was done by decreasing the pressure support by 2 cm H_2O every 4 hours, with close monitoring for worsening of SaO_2 and RR. When IPAP and EPAP were reduced to 8 and 4 cm H_2O respectively with satisfactory blood gases, pH >7.35, stable vitals, $SaO_2 \geq 90\%$ on $FiO_2 \leq 0.4$, RR <30/min, and absence of severe dyspnea/depressed sensorium, the NIPPV support was removed and patients were allowed to breathe spontaneously on a venturimask. Patients of group II received invasive PSV (by SERVO-S MACQUET ventilator system) with an initial level of pressure support that was decided on the basis of achieving acceptable ABG parameters, RR <25/min, and patient's tolerance and comfort. Subsequently, the pressure support was decreased by 2 cm H_2O every 4 hours with close monitoring for worsening of SaO_2 and RR. When the pressure support and PEEP reached 10 and 5 cm of H_2O respectively, with satisfactory blood gases, pH >7.35, stable vitals, $SaO_2 \geq 90\%$ on $FiO_2 \leq 0.4$, RR <30/min, and absence of severe dyspnea/depressed sensorium, patients were extubated and allowed to breathe spontaneously on a venturimask.

Weaning was considered 'successful' when, after two hours of spontaneous breathing on a venturimask, the patient maintained a $SaO_2 \geq 90\%$ on $FiO_2 \leq 0.4$, pH >7.35, RR <30/min, no dyspnea, intact sensorium and stable hemodynamic status. Weaning was considered a 'failure' when one or more of these criteria were absent, or if the patient could not be extubated even after 30 days of invasive MV, or had to be re-intubated within 72 hours of extubation, or if death occurred due to MV *per se*. Causes of the latter were nosocomial infection, pneumothorax, cardiac ischemia or fatal arrhythmias. Nosocomial/ventilator-associated pneumonia (VAP) was defined as the presence, during MV, of new and persistent opacities on chest X-ray along with fever and total leukocyte count (TLC) >10,000/cu mm after 48 hours of invasive MV.

The outcome variables used to compare the two groups were–duration of MV (in group I, the duration before randomization; in group II, the duration before randomization in addition to the weaning duration after randomization), duration of weaning (in both groups, the duration after randomization), duration of ICU stay (in both groups, from day of admission to day of discharge), occurrence of nosocomial pneumonia, and patient outcome in terms of survival or death at discharge.

Data are expressed as mean ± standard deviation, numbers (*n*) or percentage (%). The standard normal variate test (Z score, applicable for quantitative data) for testing the significant difference between double sample mean was applied to find the significant difference for different variables between the two groups. All the values of $Z_{calculated}$ were compared with $Z_{tabulated}$ value of 1.96 at 5% level of significance. Chi-square (χ^2) test was used for categorical data, wherever applicable. Statistical Package for Social Sciences software (SPSS Inc, Chicago IL, USA) was used for all statistical calculations. $P < 0.05$ was taken as statistically significant.

RESULTS

One hundred and fifty patients of acute exacerbation of COPD with type II respiratory failure were admitted in the ICU of our hospital during the 18 month study period. Fifteen were excluded from the study due to concomitant pneumonia ($n = 6$), lung neoplasm ($n = 5$), acute myocardial infarction ($n = 2$) and cardiogenic pulmonary edema ($n = 2$). Of the remaining 135 patients, 40 underwent direct ETI and MV. Ninety five patients were initially given a trial of NIPPV of which 25 required invasive MV within an hour of the trial. Thus, the total number of patients who needed MV and were eligible for the study were 65. Eight patients died during or immediately after ETI. Of the remaining 57 patients, seven were successfully extubated after the initial t-piece trial and were excluded. Remaining 50 patients were randomized into two groups of 25 each and compared for the outcome variables [Figure 1].

No difference was observed between the two groups in terms of demographic, clinical and biochemical parameters at the time of admission and randomization [Table 1]. Medical therapy was optimized for patients of both groups and comprised of β_2 agonists, theophylline and anti-cholinergic agents.

The initial mean IPAP and EPAP used in patients of group I were 14.79 ± 1.38 and 5.99 ± 0.73 cm of H_2O respectively. Initial mean pressure support used in patients of group II was 18.51 ± 1.23 cm of H_2O above a PEEP of 5 cm of H_2O. Statistically significant difference was found between the two groups in terms of the durations of ventilation, weaning and ICU stay [Table 2]. Occurrence of nosocomial pneumonia was also significantly lower in patients weaned by NIPPV than those by PSV (2 patients-8% *vs* 8 patients-32%, respectively) [Table 2]. Fewer deaths occurred in the ICU at discharge among group I patients than among group II patients (2 patients-8% *vs* 8 patients-32%, respectively) [Table 2]. More patients were successfully discharged from the ICU in group I than in group II (23 patients-92% vs 17 patients-68%, respectively) [Table 2].

DISCUSSION

Our study shows that NIPPV appears to be a promising weaning modality for mechanically ventilated hypercapneic COPD patients who fail an initial t-piece breathing trial.

Occurrence of bronchospasm, increased airway mucus and airway inflammation in COPD produces air trapping, diaphragmatic flattening and increased airway resistance. These in turn increase the elastic recoil, intrinsic PEEP,

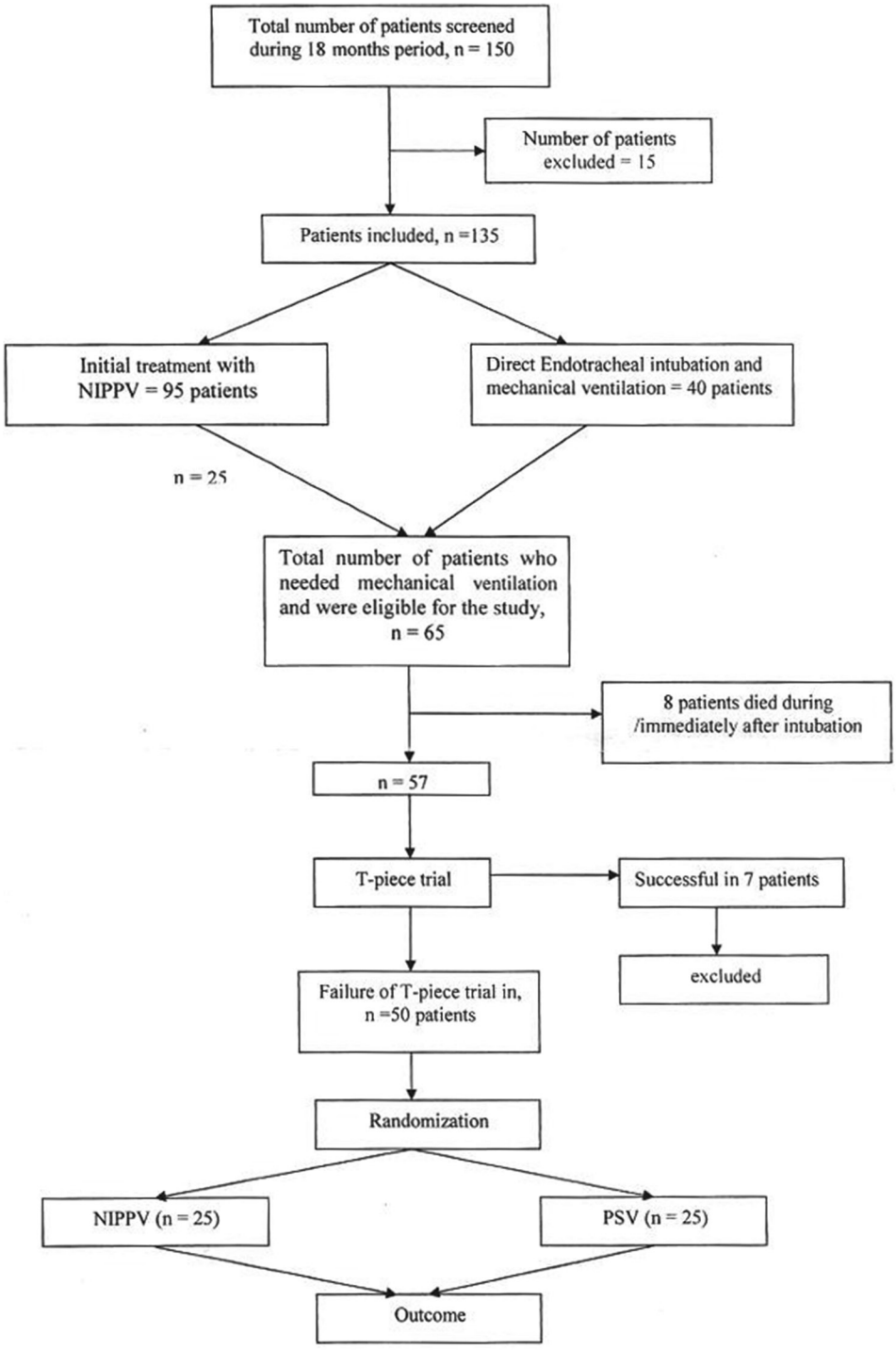

Figure 1: Methodology of patients' inclusion

work of breathing, produce muscle weakness, recruitment of accessory muscles, changes in shape of the rib-cage,[15] and ultimately respiratory muscle failure occurs.[16] These factors are responsible for prolongation of MV and weaning failure in COPD patients. During acute decompensation of COPD, the goal is to reduce carbon dioxide levels by unloading the respiratory muscles and augmenting alveolar ventilation, thereby stabilizing arterial pH until the underlying problem can be reversed.[16] NIPPV achieves this by resting the muscles of respiration thus reducing their fatigue, improving the pattern of respiration and facilitating efficient gas exchange. Thus it may be beneficial in hypercapneic respiratory failure which is frequently encountered in COPD and in weaning failure.[17,18] Role of NIPPV in acute exacerbation of COPD has been proven by previously conducted RCTs[11,19,20] and meta-analyses.[21,22] However, its use as an early weaning/extubation technique from invasive MV remains controversial.[23]

Table 1: Demographic, clinical and biochemical parameters of the two groups

	Group I	Group II	$Z_{calculated}$	$Z_{0.05}$	*P* value
Age (years)	59.92±11.89	61±8.24	1.38	1.96	>0.05
Gender					
Male	20 (80%)	18 (72%)	0.59	1.96	>0.05
Female	5 (20%)	7 (28%)	1.31	1.96	>0.05
Smoking history (pack years)	50.67±12.11	48.98±15.82	1.29	1.96	>0.05
Glasgow coma scale score	7.53±2.03	8.62±1.97	1.67	1.96	>0.05
$FEV_1\%^*$ (disease severity)	28.58±7.92	29.61±4.62	1.703	1.96	>0.05
Total leukocyte count (per cu mm)	11788.71±4851.76	12033.51±3909.7	1.213	1.96	>0.05
Mean arterial blood pressure (mmHg)	69.73±21.28	72.58±30.19	1.701	1.96	>0.05
Heart rate (beats/min)	131.05±15.01	136.18±16.87	1.806	1.96	>0.05
Respiratory rate (breaths/min)	32.1±14.97	32.67±14.68	0.927	1.96	>0.05
Arterial blood pH	7.02±0.08	7.11±0.092	1.471	1.96	>0.05
$PaCO_2$ (mmHg)	102.39±25.38	95.25±20.18	0.782	1.96	>0.05

*% forced expiratory volume at one second

Table 2: Results

	Group I	Group II	Z_{cal} or χ^2_{cal}	$Z_{0.05}$ or $\chi^2_{0.05}$	*P* value
Duration of ventilation (days)	4.93±2.92	6.90±2.97	Z_{cal}=3.98	$Z_{0.05}$=1.96	<0.05
Duration of weaning (days)	5.09±2.39	7.56±2.35	Z_{cal}=4.03	$Z_{0.05}$=1.96	<0.05
Duration of ICU stay (days)	13.18±4.85	18.11±3.65	Z_{cal}=3.77	$Z_{0.05}$=1.96	<0.05
Nosocomial Pneumonia	2 (8%)	8 (32%)	χ^2_{cal}=16.11	$\chi^2_{0.05}$=9.38	<0.05
Patients discharged	23 (92%)	17 (68%)	χ^2_{cal}=16.11	$\chi^2_{0.05}$=9.38	<0.05
Deaths in ICU	2 (8%)	8 (32%)	χ^2_{cal}=16.11	$\chi^2_{0.05}$=9.38	<0.05

$Z_{cal}=Z_{calculated}$; $\chi^2_{cal}=\chi^2_{calculated}$, ICU: Intensive care unit

There are a few studies highlighting the role of NIPPV in weaning patients with respiratory failure due to COPD. Nava *et al.*,[14] found that NIPPV reduces weaning time, shortens the time in ICU, decreases the incidence of nosocomial pneumonia, and improves 60-day survival rates, thus concluding that NIPPV is more effective than conventional PSV in weaning COPD patients from invasive MV. Gamal[24] made similar observations and concluded that noninvasive ventilation (NIV) should be considered as an early extubation and weaning technique in patients with COPD with acute-on-chronic respiratory failure who are difficult to wean. Hilbert[25] demonstrated that NIPPV was effective in correcting gas-exchange abnormalities in COPD patients with post-extubation hypercapneic respiratory insufficiency and also significantly reduced the need for ETI. Prospective RCT by Girault and associates[26] has shown that NIPPV is a useful early extubation and weaning technique in intubated acute-on-chronic respiratory failure patients who are difficult to wean. Similarly, Ferrer[27] demonstrated the efficacy of NIPPV in persistent weaning failure. Trevisan[28] concluded that the combination of early extubation and NIPPV is a useful and safe alternative for ventilation in patients who fail initial weaning attempts. Meta-analysis by Burns *et al.*,[29] demonstrated a consistent positive effect of non-invasive weaning on mortality in mechanically ventilated patients with predominant COPD. These studies suggest that use of NIPPV is associated with decreased duration of ventilatory support, length of ICU stay, incidence of VAP and survival benefit, when compared to conventional methods of weaning. In our study, the above results were confirmed and we found that NIPPV significantly reduced the duration of weaning, duration of ventilation, length of ICU stay, incidence of nosocomial pneumonia, and improved survival.

However, few studies partially or wholly contradict the above benefits of NIPPV in weaning. Girault[23] has shown that NIPPV used as an early weaning/extubation technique in difficult-to-wean patients with chronic respiratory failure did not reduce the reintubation rate within seven days as compared with conventional weaning. Nevertheless, they found that NIPPV may improve the weaning results in these patients by shortening the intubation duration and reducing the risk of post-extubation acute respiratory failure. Esteban[30] concluded that NIPPV is not effective in averting the need for reintubation in un-selected patients with post-extubation respiratory failure. Contrarily, NIPPV does not improve survival and may in fact be harmful, although selected patients in specialized centers may benefit from this therapy. Another study by Keenan[31] also showed no benefit from the addition of NIPPV to standard medical therapy in patients who develop post-extubation respiratory distress. Thus, in light of the conflicting evidence from this literature review, further large scale studies are a need of the hour to conclusively derive a consensus regarding the usefulness of NIPPV in weaning COPD patients.

The relatively higher mortality in the present study as compared to previously published studies[14,26,32] may be explained by the occurrence of VAP, as both the patients of group I and all eight patients of group II who developed VAP, subsequently expired. Greater severity of disease at presentation (as evident from low $FEV_1\%$ and GCS scores, and severe respiratory acidosis) may also be responsible

for greater mortality among our patients. VAP occurred four times lesser in patients weaned by NIPPV than those weaned by PSV in our study (2/25 *vs* 8/25, $P < 0.05$). In contrast, Nava,[14] Girault[26] and Chen[32] have respectively reported the incidence of VAP as 0/25 *vs* 7/25, 0/17 *vs* 2/16 and 0/12 *vs* 7/12 in the study *vs* control groups. Lesser occurrence of VAP in the NIPPV arm may be because NIPPV reduces the duration of exposure to artificial airway, facilitates expectoration and deglutition, thus reducing the chances of aspiration and consequent development of VAP.

Limitations of our study are that the sample size was relatively small, patients were monitored only during their ICU stay, and no data were collected after they were discharged from the ICU. Further, the study was conducted in a selected group of severely hypercapneic COPD patients, and its success in sicker patients with serious co-morbidities or severe hypoxemia merits further investigation.

To conclude, based on the shorter time needed for weaning from MV, duration of ventilation, ICU length of stay, incidence of nosocomial pneumonia and reduced mortality, NIPPV has been shown in the present study as a better weaning modality in a selected group of mechanically ventilated, hypercapneic COPD patients than conventional weaning by PSV. Thus, NIPPV should be tried in resource-limited settings especially in developing countries. However, keeping in mind the conflicting evidences observed from previously published studies,[33-36] the need for well-designed, multicenter, prospective RCTs to arrive at more reliable conclusions regarding the benefits or otherwise of NIPPV in weaning cannot but be overemphasized.

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